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Human pharmacology of 5-epi-sisomicin (Sch 22591) following intramuscular administration

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5-epi-sisomicin was given as a single intramuscular injection of 1 mg/kg to six healthy male adults. Serum peak concentrations averaged 3.07 mg/l, the mean elimination half life was 179 min and the mean 24 h urinary recovery was 85.3%. Local and systemic tolerance was good.

Introduction

5-epi-sisomicin (Sch 22591) is a semisynthetic aminoglycoside which is derived from sisomicin (Testa *et al.*, 1974). Introduction of a hydroxy group in position 5 of the deoxystreptamine ring results in an enhanced antibacterial activity against a great variety of Gram-positive and Gram-negative bacteria (Fu & Neu, 1978; Kabins & Nathan, 1978; Sanders, Sanders & Goering, 1978; Watanakunakorn, 1978). 5-epi-sisomicin is either not, or less effectively, modified by most aminoglycoside modifying enzymes (Waitz *et al.*, 1978; Vastola, Altschaeff & Harford, 1980). In addition, 5-epi-sisomicin appears to be superior to other aminoglycosides in protecting mice infected with *Pseudomonas aeruginosa* (Goering, Sanders & Sanders, 1978; Waitz *et al.*, 1978). The purpose of this study was to investigate the pharmacokinetics of 5-epi-sisomicin in humans after intramuscular injection of 1 mg/kg body weight and to evaluate local and systemic tolerance.

The results of this study have been presented previously as an extended abstract (Lüthy, Münch & Blaser, 1980). Recently data from a similar study have been reported in this Journal (Amirak *et al.*, 1985). However, some results presented in the paper by Amirak *et al.* (1985) differ substantially from the pharmacokinetic data obtained in our study. Hence, these data are presented here in detail and methodological differences between the two studies are addressed in the discussion.

Methods

Six healthy male volunteers, 21–28 years old, with a mean body weight of 69 kg (± 11.5 kg, s.d.) were enrolled in this study. The study was performed according to institutional policies, with written informed consent obtained from each participant. A dose of 1 mg/kg of 5-epi-sisomicin was injected into the upper outer quadrant of the gluteal area. Thirteen venous samples were withdrawn from an arm vein, before the administration and 15, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 12 and 24 h following the im dose. After clotting at room temperature blood samples were centrifuged at

4°C. Urine was sampled quantitatively during a 24 h period before administration of the drug and in seven fractions over a 72 h period following the injection. Serum and urine standards in the range of the expected concentrations were prepared on the study day with pooled antibiotic free human serum and 0.05 M phosphate buffer, pH 7, respectively. All standards and samples were frozen in liquid nitrogen and assayed within one week with a large plate agar diffusion method (Bennet *et al.*, 1966). Concentrations of 5-epi-sisomicin in the range of 0.5–8 mg/l were assayed in quintuplicate with *Bacillus subtilis* (spore suspension, Difco Laboratories, Detroit Michigan, U.S.A.) as the assay organism. Concentrations in the range of 0.016–0.5 mg/l were determined in quintuplicate with *Staphylococcus epidermidis* (ATCC 27626) as the assay organism. The precision of the assay was determined with ten spiked serum specimens in the range of 0.016–8 mg/l. Each of these specimens was measured five times, revealing a coefficient of variation of 5.8%.

Before and after study the following laboratory examinations were performed: haematocrit, haemoglobin, a complete blood count, erythrocyte sedimentation rate, fasting blood sugar, blood urea, nitrogen, serum creatinine, bilirubin, alkaline phosphate, transaminases, and total protein with albumin/globulin ratio. Complete urine analyses including microscopic examination were conducted. A 24 h creatinine clearance was determined before, during and after the study day.

Serum kinetics during the first 12 h after administration of the drug were analysed by an open two compartment model (Gibaldi & Perrier, 1975). The pharmacokinetic parameters of the model (volume of distribution of the central compartment V_1 , rate constants for transfer between the two compartments k_{12} and k_{21} and rate constants

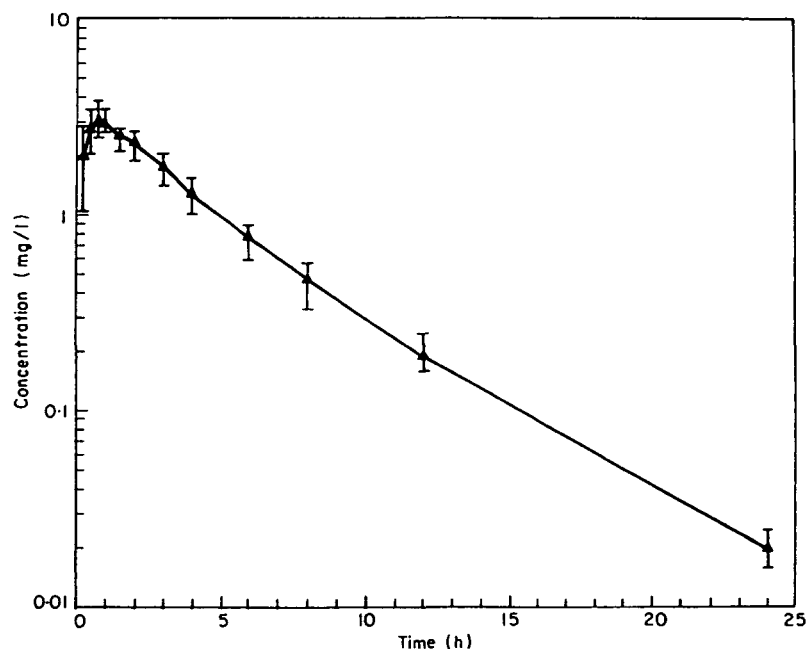


Figure 1. Mean and range of serum concentrations of 5-epi-sisomicin in six human subjects, following im administration of 1 mg/kg.

of absorption k_a and elimination k_e) were determined with a nonlinear fitting programme (Metzler, Elfring & McEwen, 1974). The total volume of distribution (V_{dss}), body clearance (Cl_b) and elimination half life ($T_{1/2}$) were defined as follows:

$$V_{dss} = V_1 * (1 + k_{12}/k_{21}); Cl_b = k_e * V_1; T_{1/2} = \ln 2/k_e.$$

Results

Serum kinetics of 5-epi-sisomicin are shown in Figure 1. Peak serum levels (\pm S.D.) averaged 3.07 ± 0.44 mg/l. The maximal concentrations were measured between 45 and 90 min after administration. The individual serum concentrations are given in Table 1. In five out of the six subjects 24 h serum concentrations were still above the sensitivity limit of the assay (0.016 mg/l), with an average concentration of 0.02 mg/l. Analysis of the serum data from the first 12 h revealed a mean serum half life of 179 ± 20 min, a total volume of distribution of 15.9 ± 1.91 (0.23 ± 0.03 l/kg) and a body clearance of 78.4 ml/min per 1.73 m² body surface area (84.3 ± 16 ml/min), respectively. The half life of absorption from the muscular depot was determined as 46 ± 13 min.

Urinary recovery averaged 83.1% (range 79.6–89.3%) for the first 12 h and 92.2% (88.7–99.5%) for the first 72 h (Figure 2). The urinary excretion rate decreased exponentially from 15.5% of the dose per hour in the first 4 h interval to less than 0.2%/h after 12 h. From 36 to 72 h the hourly excretion rate remained constant at a level of 0.1% of the administered dose. These data suggest a continuing excretion beyond the last collection period.

One patient had diarrhoea one day after drug administration, two reported dull pressure in the head for less than 12 h and one subject reported a faint pressure in both ears lasting 15 min. No significant changes in the haematology, serum chemistry or urine analysis were recorded. No local side effects attributable to 5-epi-sisomicin were recorded.

Discussion

The serum kinetics of 5-epi-sisomicin were studied in six healthy volunteers. Compared to other aminoglycoside antibiotics the peak concentrations of 3.07 mg/l following im doses of 1 mg/kg were rather low (Gruenwaldt *et al.*, 1976; Riff & Moreschi, 1977). However, Meyers *et al.* (1976) also observed peak levels of 3.08 mg/l for sisomicin. Amirak *et al.* (1985) reported for 5-epi-sisomicin a mean peak concentration of 4.82 mg/l which is 57% higher than that found in the present study. This discrepancy might be explained in part by the fact that in the study of Amirak *et al.* (1985) the standards were prepared in horse serum as opposed to pooled human serum in the present study. The mean volume of distribution of 5-epi-sisomicin (0.23 l/kg) is comparable to data reported for other aminoglycosides (Schentag *et al.*, 1977; Blaser *et al.*, 1983a, b).

The serum concentrations declined within the first 12 h after the dose according to a mean serum half life of almost 3 h. This is longer than half lives reported for other aminoglycosides in healthy young subjects (Gruenwaldt *et al.*, 1976; Blaser *et al.*, 1983a). The glomerular filtration rate of the six subjects was normal, with a mean creatinine clearance of 137 ml/min and serum creatinine values between 0.7 and 1.1 mg/100 ml. Amirak *et al.* (1985) reported a mean serum half life for 5-epi-sisomicin of 2.3 h. However, these data were derived only from serum concentrations measured

Table I. Serum concentrations of 5-epi-sisomicin (mg/l) in six human volunteers following im administration of 1.0 mg/kg

Subject	Time after drug administration (h)											
	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24
1	2.58	3.02	3.33	2.91	2.59	2.30	1.73	1.22	0.86	0.57	0.25	0.025
2	1.68	2.38	2.70	2.73	2.51	2.56	2.04	1.29	0.70	0.45	0.20	0.016
3	2.85	3.46	3.81	3.45	2.84	2.33	1.77	1.53	0.78	0.47	0.19	0.023
4	2.00	2.90	2.80	3.15	2.70	2.26	1.58	1.27	0.88	0.54	0.18	0.020
5	1.70	2.50	2.67	2.74	2.10	1.88	1.40	1.00	0.59	0.33	0.16	<0.016
6	1.04	2.05	2.48	2.63	2.68	2.64	2.04	1.44	0.79	0.48	0.18	0.017

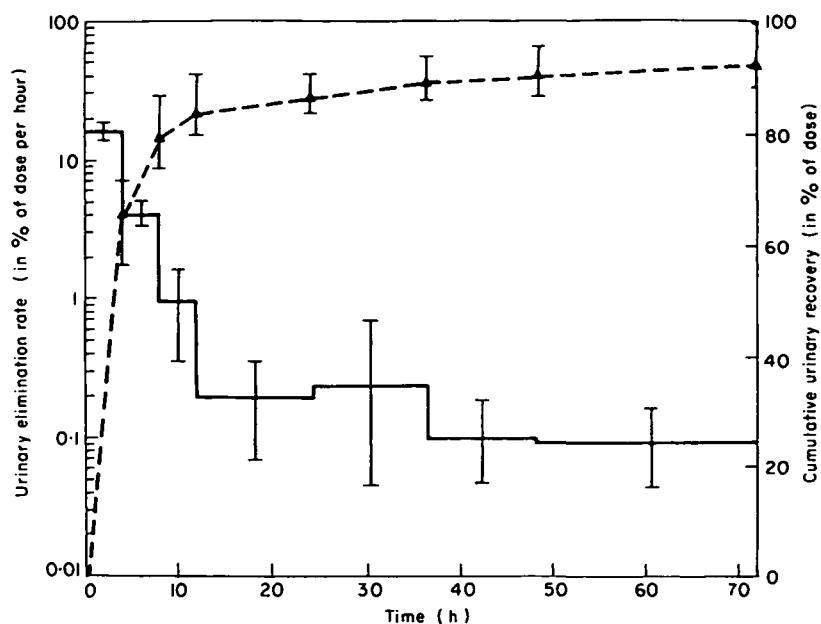


Figure 2. Mean and range of urinary elimination rate (full line, left hand scale) and cumulative urinary recovery rate (broken line, right hand scale) in six human subjects, following im administration of 1 mg/kg.

within the first 4 h after dosing. After this time the serum levels fell below the detection limits (> 1 mg/l) of the assay used in their study. The low sensitivity limit of the assay used in the present study (0.016 mg/l) allowed us to determine serum levels for up to 24 h after the administration of the dose.

However, the analysis of the serum data by means of a two compartment open model was limited to the 12 h period after drug administration. The 24 h serum concentrations had to be excluded because they were consistently higher than expected according to the half-life of elimination found during the first 12 h (Figure 1). For simulations over a longer time period a three compartment model would be needed. This finding is consistent with the concept of the presence of a deep compartment in which aminoglycoside antibiotics accumulate in the course of therapy (Schentag *et al.*, 1977; Blaser *et al.*, 1983a, b). The urinary excretion data strongly support this concept. After a distinct exponential decline of the urinary excretion rate during the initial 12 h period, the renal elimination remains fairly constant during the following 60 h. These data suggest the existence of a deep compartment which releases the accumulated drug at the rate of approximately 0.1% of the administered dose per hour. The urinary recovery rate of $92.2 \pm 4.8\%$ (mean \pm s.d.) after 72 h together with the finding of the prolonged elimination which appears to continue beyond 72 h suggest that no significant non-renal elimination occurs.

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